Invasive mechanical ventilation in patients with fibrosing interstitial pneumonia

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Objective: The prognosis of patients with idiopathic pulmonary fibrosis or fibrosing idiopathic nonspecific interstitial pneumonia undergoing invasive mechanical ventilation (MV) for acute respiratory failure is known to be poor. The issue of life support in these patients needs to be reconsidered in light of changes during the past decade in ventilator settings and in the management of acute exacerbation. We therefore aimed to reassess the prognosis of such patients.

Methods: We retrospectively assessed the outcomes of all medical patients with idiopathic pulmonary fibrosis or fibrosing idiopathic nonspecific interstitial pneumonia who required invasive MV in 3 university hospitals in the Paris area from January 2002 to April 2009.

Results: In total, 27 patients (mean age, 66 ± 12.8 years) required invasive MV in the intensive care unit: 8 (30%) were successfully weaned from MV, and 6 and 4 were discharged from the intensive care unit and the hospital, respectively. Survivals for patients who did not undergo lung transplant were 22%, 3.7%, and 3.7%, at 30 days, 6 months, and 12 months, respectively.

Conclusions: We confirm that use of invasive MV for acute respiratory failure in patients with idiopathic pulmonary fibrosis or fibrosing idiopathic nonspecific interstitial pneumonia is associated with a high mortality; however, a subset of patients may be discharged alive from the intensive care unit and hospital, providing an opportunity to consider lung transplant in case of eligibility. Our results suggest that invasive MV should not be systematically denied to these patients but discussed on a case-by-case basis. (*J Thorac Cardiovasc Surg* 2014;147:47-53)

The prognosis is poor for the most common idiopathic fibrosing interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (iNSIP) in its fibrotic form. In particular, the median survival after diagnosis of IPF is 2 to 3 years.¹ The clinical courses of IPF and iNSIP are usually slowly progressive but may be complicated by episodes of acute deterioration. During an episode of acute respiratory failure

(ARF), the patient's condition may worsen despite symptomatic treatment, possibly leading to referral to an intensive care unit (ICU) and the requirement of invasive mechanical ventilation (MV). Guidelines concerning the referral to the ICU and initiation of MV are lacking; however, the literature suggests that invasive MV for patients with IPF is appropriate when respiratory failure follows a surgical procedure but is questionable for medical patients because the short- or medium-term outcome is poor, according to several convergent studies.²⁻⁷ This has led many intensivists to deny initiation of invasive MV in this setting⁸; however, most studies investigating outcomes after MV in fibrotic lung diseases involved patients who underwent MV back in the 1990s.

We aimed to reassess the prognosis of medical patients with idiopathic fibrosing interstitial pneumonias (IPF and iNSIP) who required invasive MV in the ICU. Our hypothesis was that the prognosis of these patients might have improved with time, at least with respect to the short-term (ICU) mortality because of developments in the past decade in ventilator settings and management of acute exacerbation in patients undergoing MV, as suggested in a recently published letter.⁹ This question seems relevant because an improvement in even short-term prognosis could

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Abbreviations and Acronyms

ARF	= acute respiratory failure
BAL	= bronchoalveolar lavage
ECMO	= extracorporeal membrane oxygenation
ICU	= intensive care unit
IPF	= idiopathic pulmonary fibrosis
iNSIP	= idiopathic nonspecific interstitial pneumonia
LTx	= lung transplant
MV	= mechanical ventilation
V _T	= tidal volume

allow access to lung transplant (LTx) for patients who are eligible for this procedure.¹⁰ We conducted a retrospective study of patients with IPF in the ICUs of 3 university hospitals. We also investigated patients with fibrosing iNSIP because of their similarities in terms of clinical decision making at the time of admission to an ICU.

MATERIALS AND METHODS

This was a retrospective study of patients in 3 ICUs of teaching hospitals in the Paris area, particularly hospitals involved in care of interstitial pulmonary diseases (Bichat Hospital, Avicenne Hospital, Hôtel Dieu Hospital). We analyzed the medical charts of all patients with fibrosing idiopathic interstitial pneumonia (IPF or fibrosing iNSIP) who required invasive MV from January 2002 to April 2009. This study was approved by the ethics committee of the Société de Réanimation de Langue Française (project 08-263, June 18, 2009).

The diagnosis of IPF was based on histologic evaluation (surgical lung biopsy, transbronchial biopsy, or autopsy) indicative of usual interstitial pneumonia and the absence of an identifiable cause (professional exposure, drug toxicity, identified connective tissue disease). In the absence of histologic evaluation, patients had to fulfill all major criteria and at least 3 of the 4 minor criteria of the American Thoracic Society (ATS) and European Thoracic Society.¹¹ Diagnosis of fibrosing iNSIP was based on a histologic evaluation indicative of a fibrotic pattern of nonspecific interstitial pneumonia in the absence of an identifiable cause (drug toxicity, infection, connective tissue disease) as proposed by the consensus conference of the American Thoracic Society and European Respiratory Society published in 2002.¹ Invasive MV was defined as the use of MV through an endotracheal tube (orotracheal, nasotracheal intubation, or tracheostomy). All selected patients had undergone invasive MV for ARF or hemodynamic failure. Patients with MV who were admitted to the ICU for simple monitoring after a surgical procedure or a bronchoscopy were excluded.

Data Gathering

We recorded data from medical charts.

Characteristics of patients at baseline. Baseline data included age, sex, body mass index, smoking habit, comorbidities (ischemic heart disease, systemic hypertension, and diabetes), diagnosis (IPF or fibrosing iNSIP), type of histologic evidence if available, disease duration, results from most recent pulmonary function tests (including vital capacity, total lung capacity, ratio of forced expiratory volume in 1 second to vital capacity, carbon monoxide diffusing capacity), blood gas analysis, pulmonary hypertension at baseline (defined as mean pulmonary arterial pressure >25 mm Hg at the right heart catheterization or arbitrarily as systolic pulmonary arterial pressure >50 mm Hg when measured by echocardiography at rest¹²), requirement of long-term oxygen therapy, use of

corticosteroids or immunosuppressive therapy at the time of admission, curative anticoagulation therapy, and registration on a waiting list for LTx.

Characteristics on admission to the ICU. ICU admission data included Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation II score, and reason for ICU admission.

Management in the ICU. ICU management data included time elapsed between admission and the beginning of invasive MV, use of noninvasive ventilation before intubation, ventilator settings after intubation (ventilation mode, tidal volume [V_T] expressed in mL/kg ideal body weight, level of positive end-expiratory pressure, plateau pressure), need for systemic catecholamines within 24 hours after intubation, best Pao₂/fraction of inspired oxygen ratio and best Paco₂ within 24 hours after intubation, type of microbiologic respiratory sampling if available obtained before or soon after intubation (bronchoalveolar lavage [BAL], protected distal sampling, tracheal aspirate), type of antibiotics received after admission in the ICU, use of high-dose intravenous “pulse” methylprednisolone, introduction of immunosuppressive drugs, use of curative anticoagulation therapy, treatment with N-acetylcysteine, use of inhaled nitric oxide after intubation, requirement of extracorporeal membrane oxygenation (ECMO) at any time during the ICU stay, weaning from MV, performance of LTx during the ICU stay, and discharge from versus death in the ICU.

Characteristics after the ICU stay. Data collected after the ICU stay included discharge from the hospital versus death in the hospital and LTx.

Survival. Survivals were determined at 30 days, 6 months, and 12 months after ICU admission.

Data Review

Clinical, biologic, and radiologic data were reviewed retrospectively by 2 investigators (S.G. and H.M.) to determine the cause of admission to the ICU. The diagnosis of bacterial pneumonia was based on radiographic evidence of new infiltrates and significant concentration of bacteria in respiratory specimens (>10⁴ colony-forming units/mL on BAL, >10³ colony-forming units/mL on protected distal sampling, >10⁶ colony-forming units/mL on tracheal aspirate). Diagnosis of *Pneumocystis* pneumonia was based on the presence of *Pneumocystis jirovecii* in BAL fluid. Diagnosis of acute exacerbation of IPF was based on criteria defined by Collard and colleagues¹³: (1) onset or recent increase of dyspnea (<30 days), (2) appearance of ground-glass opacities or superimposed condensation on preexisting reticular opacities and honeycombing, (3) absence of infectious precipitating factor, and (4) absence of another identifiable cause (eg, heart failure, pulmonary embolism, pneumothorax).

Successful weaning from MV was defined as extubation or ability to breathe spontaneously for 24 hours on tracheostomy cannula. ICU survival and hospital survival were defined as discharge of the patient from the ICU and hospital, respectively.

Statistical Analysis

Statistical analysis involved use of GraphPad Prism 5 (GraphPad Software, San Diego, Calif). Categorical data are described by number and percentage and were compared by χ^2 test. The distribution of continuous data was tested by the Kolmogorov-Smirnov test. Continuous data with normal distribution are described by mean $\pm$ SD and were compared with the Student *t* test. Continuous data with nonnormal distribution are described by median with interquartile range (25%-75%) and were compared with the Mann-Whitney *U* test. The Kaplan-Meier estimator was used to estimate survival.

RESULTS**Baseline Characteristics of Patients**

Baseline patient characteristics were determined by analysis of charts for 27 patients (23 men; mean age,

66.6 ± 12.8 years) (Table 1). Among these patients, histories included smoking (past or active) in 17 cases (63%), diabetes in 6 (22%), ischemic heart disease in 5 (19%), and systemic hypertension in 9 (33%). At the time of admission, all patients already had an established diagnosis of IPF or fibrosing iNSIP. Histologic evidence was available for 10 patients (37%; surgical biopsies, n = 7; postmortem examination, n = 2; transbronchial biopsy, n = 1). Overall, 22 patients (81.5%) had IPF and 5 (18.5%) had fibrosing iNSIP. The median delay between symptom onset and admission to the ICU was 1.9 years (interquartile range, 1.1-3.8 years).

Pulmonary function tests performed at baseline showed a restrictive syndrome in all patients, with mean total lung capacity 50.7% ± 13.6% predicted and mean vital capacity 53.3% ± 15.4% predicted. Mean carbon monoxide diffusing capacity was 29.7% ± 12.8% predicted. In total, 7 patients (26%) had pulmonary hypertension, 15 (55%) were receiving long-term oxygen therapy, 2 were on a waiting list for LTx, 17 (63%) were receiving long-term corticosteroids, 9 (33%) were receiving immunosuppressive therapy combined with corticosteroids (azathioprine, n = 5; cyclophosphamide, n = 2; mycophenolate mofetil, n = 2), and 4 (15%) had curative anticoagulation before hospitalization.

Characteristics and Management in the ICU

ICU characteristics and management were determined for all 27 patients (Table 2). All were admitted to an ICU for ARF. Mean Simplified Acute Physiology Score II and

TABLE 1. Characteristics of patients

Age (y)	66.6 ± 12.8
Male sex (No.)	23 (85%)
Body mass index (kg/m ²)	26.1 ± 4.7
IPF/iNSIP case ratio	22/5
Histologic confirmation of diagnosis (No.)	10 (37%)
Duration of disease progression (y, median and IQR)	1.9 (1.1-3.8)
Long-term oxygen therapy (No.)	15 (55%)
Pulmonary arterial hypertension (No.)	7 (26%)
Paco ₂ baseline (mm Hg)	41 ± 6.4
Total lung capacity (% predicted)	50.7% ± 13.6%
VC (% predicted)	53.3% ± 15.4%
FEV ₁ /VC (%)	84.3% ± 9.7%
DLCO (% predicted)	29.7% ± 12.8%
DLCO/VA (% predicted)	68.9% ± 21.5%
On waiting list for transplant (No.)	2 (7%)
Long-term corticosteroid treatment (No.)	17 (63%)
Immunosuppressive therapy (No.)	9 (33%)
Curative anticoagulation (No.)	4 (15%)
History of previous acute exacerbation (No.)	5 (19%)

Data are mean ± SD unless indicated. IPF, Idiopathic pulmonary fibrosis; iNSIP, idiopathic nonspecific interstitial pneumonia; IQR, interquartile range; VC, vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, carbon monoxide diffusing capacity; VA, alveolar volume.

TABLE 2. Management of patients in intensive care unit

Tidal volume (mL/kg predicted body weight)	5.9 ± 1.3
PEEP (cm H ₂ O)	7.1 ± 3.3
Inhaled nitric oxide (No.)	9 (33%)
Plateau pressure (cm H ₂ O, n = 14)	33.4 ± 7.3
Respiratory samples (No.)	27 (100%)
Bronchoalveolar lavage	17
Protected distal sampling	8
Tracheal aspiration	2
Steroid pulse (No.)	13 (48%)
Cyclophosphamide (No.)	2 (7%)
Empirical antibiotic therapy (No.)	24 (89%)
Effective anticoagulation (No.)	12 (44%)
Before ICU admission	4
During ICU stay	8
For acute exacerbation	7
For pulmonary embolism	1
N-acetylcysteine (No.)	4 (15%)
ECMO (No.)	2 (7%)

Data are mean ± SD unless indicated. PEEP, Positive end-expiratory pressure; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.

mean Acute Physiology and Chronic Health Evaluation II scores were 47 ± 24 and 22 ± 11, respectively, for the whole cohort. In total, 17 patients (63%) were intubated within the first 24 hours and 19 (70%) underwent noninvasive ventilation sessions before intubation. On the day of intubation, 19 patients (70%) had hemodynamic failure requiring intravenous catecholamines. Most patients, 22 (81%), underwent contrast-enhanced computed tomography of the thorax during hospitalization. In the early days of the ICU stay, all patients underwent respiratory sampling to search for an infectious cause (BAL, n = 17; protected distal sampling, n = 8; tracheal aspiration, n = 2).

The cause of ARF was identified in 24 patients (89%): acute exacerbation of fibrosis (n = 14, 52%), lower respiratory tract infection (n = 5, 19%), pulmonary embolism (n = 1), septic shock (n = 2, pyelonephritis and acute infectious colitis n = 1 each), bronchioloalveolar carcinoma (n = 1), and hemorrhagic shock (n = 1). Among the 5 respiratory tract infections, 4 were bacterial (*Pseudomonas aeruginosa*, n = 2; *Streptococcus pneumoniae*, n = 1; *Staphylococcus aureus*, n = 1) and 1 fungal (pneumocystosis).

After intubation, all patients were sedated and receiving volume assist-control ventilation (mean, V_T 5.9 ± 1.3 mL/kg; mean positive end-expiratory pressure, 7.1 ± 3.3 cm H₂O). The corresponding mean plateau pressure at day 0 was 33.4 ± 7.3 cm H₂O (data available for 14 patients). Blood gas analysis performed within 6 hours after the initiation of invasive MV showed profound hypoxemia (mean Pao₂/fraction of inspired oxygen ratio, 135 ± 72) and hypercapnia (mean Paco₂, 60 ± 18 mm Hg). In total, 9 patients (33%) received inhaled nitric oxide during the period of invasive MV. Two patients required ECMO while

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waiting for LTx. Before the results of microbiologic sampling, 24 patients (89%) received empirical antibiotic therapy (most often broad-spectrum antibiotic therapy). Among 14 patients with acute exacerbation of fibrosis, 13 received high-dose intravenous “pulse” methylprednisolone in the ICU. In addition, 2 patients received intravenous cyclophosphamide. Among the 23 patients who were not receiving curative anticoagulation before hospitalization in the ICU, 8 received curative unfractionated heparin (7 because of acute exacerbation of fibrosis and 1 because of pulmonary embolism).

During the ICU stay, ventilator-acquired pneumonia developed in 3 patients, and 2 had pneumothorax.

Outcomes

Outcomes are shown in Figure 1. Of the 27 patients, 20 died in the ICU, including 1 undergoing ECMO. The causes of death were as follows: refractory hypoxemia ($n = 13$), multiorgan failure related to sepsis ($n = 6$), and intracerebral hemorrhage (in the patient undergoing ECMO). One patient underwent LTx during ECMO. In total, 8 patients (30%) were successfully weaned from invasive MV, 1 after undergoing tracheostomy for weaning purposes. Of these 8 patients, 2 subsequently died while in the ICU and 6 (22%) were discharged from the ICU (5 with IPF and 1 with fibrosing iNSIP).

The median duration of invasive MV in the 6 patients discharged alive from the ICU was 5.5 days (interquartile range 3.5-14.7). The causes of ARF in these 6 patients were lower respiratory tract infection ($n = 3$), acute exacerbation of fibrosis ($n = 2$), and unidentified ($n = 1$).

Two patients died in the general hospital ward after discharge from the ICU (cardiac arrest $n = 1$, new episode of ARF related to the evolution of fibrosis $n = 1$), and 4 were discharged alive from the hospital. Two of these 4 underwent LTx after their respiratory condition improved after pulmonary rehabilitation, 1 died within 6 months after hospital discharge because of evolution of pulmonary fibrosis, and 1 was still alive 1 year after ICU admission.

Survivals for patients who did not undergo LTx were 22%, 3.7%, and 3.7% at 30 days, 6 months, and 12 months, respectively (Figure 2).

DISCUSSION

We aimed to evaluate the prognosis of patients with fibrosing idiopathic interstitial pneumonia who required invasive MV for ARF in 3 Paris hospitals. Most patients requiring invasive MV for acute deterioration of their respiratory condition died while undergoing treatment in the ICU. A subset of patients could be discharged alive from the ICU; however, we found that their 6-month mortality was high.

Several studies of medical patients have previously analyzed the outcomes of patients with IPF admitted to an ICU for respiratory failure.²⁻⁷ Most studies involved patients who underwent MV in the 1990s. The results of these studies, characterized by a retrospective design (like ours) and small sample size (14 to 25 patients), were convergent and showed a dismal prognosis. Except for patients who underwent LTx, the mortality in the ICU was 100% in almost all studies. In 1 study, 17% of patients could be discharged from the ICU; however, half

FIGURE 1. Outcomes of patients with fibrosing idiopathic interstitial pneumonia invasively ventilated in intensive care unit (ICU).

FIGURE 2. Kaplan-Meier survival curve of patients with fibrosing idiopathic interstitial pneumonia and invasive ventilation. Note that data of the patient who underwent lung transplant before day 30 were censored at the time of transplant.

died shortly thereafter.² These results have led many intensivists to consider that initiation of invasive MV is futile in this setting and that only noninvasive ventilation should be used.¹⁴

Our study of patients requiring invasive MV a decade later yielded similar results in terms of overall prognosis; however, we identified a subgroup of 6 patients (22%) who could be discharged alive from the ICU, thus delaying the date of death. These results cannot be explained by a difference in terms of baseline severity of the disease, because our patients' characteristics (age, results of recent pulmonary function tests, and requirement of long-term oxygen therapy) are comparable to those in older series. In line with our results, a recently published letter has suggested that the prognosis of patients admitted to the ICU for ARF and receiving MV may have changed in recent years. This study showed a better short-term prognosis (30-day survival) for patients who received MV from 2005 to 2009 than for those treated from 1999 to 2004. That study, however, mixed patients receiving noninvasive and invasive MV and did not describe the ventilator settings, such as V_T and plateau pressure.

Even if we are now able to provide a short-term survival benefit for some patients, our data are in line with the general perception that initiating MV for ARF in patients with IPF is highly questionable, because most patients died within 6 months. We believe, however, that the situation is somewhat different if the patient can be considered for LTx. Indeed, LTx is effective in improving the survival of selected patients with IPF.¹⁵ In selected patients who fulfill the criteria for LTx, invasive MV may be used as a bridge to the procedure. The aim of invasive MV would be to prevent immediate death from ARF and to stabilize the cardiorespiratory condition for a time, thus allowing the recipient to wait for an adequate organ.

In this setting, invasive MV may be used alone or in association with ECMO. This bridging strategy, which is being followed increasingly for selected patients with lung fibrosis and ARF, is associated with a worse prognosis than standard LTx,¹⁶⁻¹⁸ but it can provide a real chance of survival for patients who would probably have died otherwise.^{18,19} The most recent studies evaluating ECMO as a bridge to LTx have yielded very encouraging results.^{20,21} Moreover, the interesting option of ambulatory ECMO could allow patient physical rehabilitation before LTx.^{21,22} In the study by Hoopes and colleagues,²¹ out of 31 patients who underwent ECMO as a bridge to LTx, 19 were ambulatory at the time of LTx. Another promising option that allows pretransplant rehabilitation is ECMO in awake, nonintubated patients.²³

The modification of allocation rules implemented in the United States and Europe now allows performance of LTx within several days or weeks in the most severe cases.^{18,19,24} The short-term survival benefit we observed with MV in some patients, by delaying the date of death, could potentially allow an increased probability of receiving a lung for LTx. Only 1 patient in our series underwent emergency LTx while undergoing invasive MV, which did not influence our ICU survival results because that patient was excluded from the survival analysis. LTx may also be performed well after discharge from the ICU, as was the case for 2 of our patients. Nevertheless, even if LTx can be performed while the patient is undergoing MV or shortly thereafter, it should ideally be performed earlier in the course of the disease and the patients referred to a transplant center as soon as the diagnosis is made, as recommended by the guidelines of the International Society of Heart and Lung Transplantation.¹⁰

Several factors could explain the apparent short-term survival benefit observed for some patients, even though our data do not allow us to draw any conclusions. First, the high rate of identification of the cause of ARF (89%) contrasts with that from the previous studies, in which a cause was unidentified in approximately half of the cases. One might hypothesize that this high rate of identification has led to appropriate treatment of treatable causes. Second, all patients with acute exacerbation of IPF or iNSIP received steroid pulses, and most received anticoagulant therapy. Despite the absence of blinded, controlled studies, a benefit provided by these treatments has been advocated.²⁵ Third, a difference in ventilator settings (low V_T , use of a volume-driven ventilator mode [assist control]) could be involved, even if it is important to remember that no "safe setting" exists.²⁶ In particular, V_T has been substantially decreased during the last decade in patients with reduced pulmonary compliance. In light of the proven benefit of a low- V_T approach (6 to 8 mL/kg body weight) in acute respiratory distress syndrome, similar ventilator settings were probably used for our patients, as evidenced

by the mean V_T value in our study (5.9 ± 1.3 mL/kg body weight). By contrast, V_T ranged from 8 to 13 mL/kg body weight in previous studies.^{2,3,27} In addition to a possible beneficial effect of a low V_T , asynchrony between ventilator cycle and spontaneous breathing could result in higher ventilator-induced lung injury. Asynchrony is not likely to have occurred in our patients, however, because the 3 experienced centers involved in this study largely use profound sedation and neuromuscular blocking agents in the management of such patients. Despite a low V_T , mortality was high among our patients. We hypothesize, that despite an expected decrease in ventilator-induced lung injury, our patients had very advanced pulmonary fibrosis, which explains the high mortality. Furthermore, the plateau pressure of our patients was still in a relatively high range, with a possible superimposed deleterious effect on the lungs.²⁸ In addition to ventilator settings, neuromuscular blockers, which are commonly used in all 3 centers, may also have played a role in the short-term benefit observed in some patients,^{29,30} even though we have not specifically retrieved the information concerning the use of such agents in our patients.

Our study contains some limitations. The first is its retrospective design. Other limitations are the relatively low number of patients included and the long span between the beginning and end of the patient inclusion. The diagnosis of the cause of ARF may have been missed in some cases because our diagnostic evaluation was not exhaustive. For example, the search for *P jirovecii* was based on direct examination of BAL fluid rather than polymerase chain reaction, and the presence of viral infection was not investigated. Drug toxicity was not suspected, but obviously this diagnosis is difficult to rule out in this setting. Our mixing of patients with IPF and iNSIP could have introduced a bias toward improved prognosis, even though we found no difference in prognosis between patients with IPF and fibrosing iNSIP.

CONCLUSIONS

In conclusion, our data suggest that the prognosis of patients with IPF or fibrosing iNSIP undergoing invasive MV for ARV, at least in the short term, may have changed during the last decade. We found a subset of patients who could be discharged alive from the ICU, thus providing a potential opportunity to consider LTx in case of eligibility.

We confirm, however, that the use of invasive MV for such patients remains associated with high mortality, because most patients who did not undergo LTx died within 6 months. Our results are in line with the general belief that patients do not benefit from invasive MV in this setting. On the basis of our results, we think that initiation of invasive MV for patients with fibrosing IPF and iNSIP should be discussed on case-by-case basis.

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